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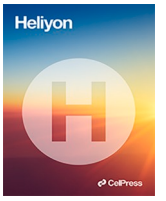

Review article

Ferroptosis-related oxaliplatin resistance in multiple cancers: Potential roles and therapeutic Implications

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ABSTRACT

Oxaliplatin (OXA)-based therapy is effective in the treatment of multiple cancers. However, primary or acquired OXA resistance remains an emerging challenge for its clinical application. Ferroptosis is an iron-dependent mode of cell death that has been demonstrated to play an essential role in the chemoresistance of many drugs, including OXA. In particular, dysregulation of SLC7A11-GPX4, one of the major antioxidant systems of ferroptosis, was found in the OXA resistance of colorectal cancer (CRC) and hepatocellular carcinoma (HCC). In addition, Nrf2, the upstream regulator of GPX4 and many other antioxidant factors, is also involved in the OXA resistance of CRC and HCC. Inhibition of SLC7A11-GPX4 or Nrf2 by genetic deletion of pharmaceutical inhibition could significantly reverse OXA resistance. Long noncoding RNA (lncRNA) also participates in chemoresistance and ferroptosis of cancer cells. Specifically, LINC01134 promotes the recruitment of Nrf2 to the promoter of GPX4, thereby exerting transcriptional regulation of GPX4, which eventually increases the OXA sensitivity of HCC through upregulation of ferroptosis. On the other hand, a novel lncRNA DACT3-AS1 sensitizes gastric cancer cells to OXA through miR-181a-5p/sirtuin 1(SIRT1)-mediated ferroptosis. Therapies based on ferroptosis or a combination of OXA and ferroptosis enhancers could provide new therapeutic insights to overcome OXA resistance. In the present review, we present the current understanding of ferroptosis-related OXA resistance, highlight ferroptosis pathogenesis in OXA chemoresistance, and summarize available therapies that target OXA resistance by enhancing ferroptosis.

1. Introduction

Since the approval by the Food and Drug Administration of the United States for application for colorectal cancer (CRC) in 2002, oxaliplatin (OXA), the third-generation platinum analog, has been widely applied for CRC, pancreatic cancer, biliary tract cancer and several other tumors [1–7]. Mechanistically, OXA binds to DNA and forms crosslinks to inhibit DNA replication and transcription, leading to significant DNA double-strand breaks (DSBs), cell apoptosis, and eventual death of tumor cells [8]. Unfortunately, intrinsic or acquired resistance of OXA has become one of the leading causes for treatment failure of cancer patients, and approximately 20–24

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% of patients respond to OXA as first-line therapy, while OXA as second-line therapy has response rates of only 10 % [9]. Therefore, it is important to elucidate the specific molecular mechanisms by which tumor cells develop resistance to OXA and to develop therapies to minimize resistance. [10].

Introduced by Stockwell in 2012, ferroptosis is an iron-dependent mode of cell death that is mechanically different from autophagy, apoptosis and necrosis [11–15]. In recent years, the essential role of ferroptosis in various diseases, including cancer [11,16–18], neurodegenerative diseases [16,19], metabolic diseases [20], and cardiovascular diseases [21–23] has been widely recognized. Morphologically, mitochondrial abnormalities in ferroptotic cells include cristae reduction, shrinkage, outer membrane disruption, and increase in membrane density [11,16,24,25]. Caused by accumulated lipid peroxides on the cell membranes, ferroptosis is mainly predominated by oxidation, antioxidant systems and iron homeostasis [11,17,26–29].

Recently, emerging evidence indicated an essential involvement of ferroptosis in OXA resistance, which gained enormous attention in cancer research [30–32]. An abnormality in the SLC7A11-GSH-GPX4 pathway has been shown to regulate OXA resistance in multiple types of cancers. Importantly, the upstream regulator of GPX4, Nrf2, which also functions as a regulator of several other antioxidant factors, also participates in the above-mentioned process. Interestingly, lysyl oxidase-like 3 (LOXL3), stearoyl coenzyme A desaturase-1 (SCD1), and several long noncoding RNAs (lncRNAs) also contribute to OXA resistance via regulating ferroptosis. Given the potential role of ferroptosis in OXA resistance, new therapies targeting ferroptosis have been developed, which may provide insights into reversing OXA resistance.

While previous reviews focus on multiple chemodrugs [33–36], our review specially put an emphasis on OXA and attempt to provide a more comprehensive introduction to the specific role of ferroptosis in OXA-resistance. On the other hand, plenty of valuable studies published in the past five years offer novel insights concerning the role of ferroptosis on OXA-resistance of cancers [37–44]. In the present review, we mainly summarize up-to-date progress underlying the mechanism of ferroptosis in OXA resistance (Table 1) and

Table 1
Changes and roles of ferroptosis regulators in OXA-resistant cancers.

Cancer type	Regulators of ferroptosis	Mechanism	Study subject	Publication year	Reference
CRC	SLC7A11	SLC7A11 upregulation induced by MTTP/PRAP1 complex promoted OXA-resistance	Obece mice xenograft model injected with MC38 cells; HCT116 and SW480 cells; Colorectal cancer organoids derived from CRC patients	2022	[58]
		SLC7A11 inhibition induced by butyrate supplementation reversed OXA-resistance and ferroptosis-resistance	HCT116, SW480, SW620 and RKO cells; nude mouse xenograft model injected with HCT116, SW480 cells; Colorectal cancer organoids derived from CRC patients	2023	[76]
	GPX4	Upregulation of GPX4 induced OXA resistance; Inhibition of GPX4 by FIN56 or siRNA reversed OXA resistance	Caco-2 and HT-29 OXA-resistant cells	2023	[63]
		NUAK1 silence or Nrf2 agonist inhibited Nrf2 expression, and thus suppressing GPX4, eventually blocked OXA-resistance	HCT116 acquired OXA-resistant cells, H716 cells (congenital OXA-resistance) and nude mouse xenograft model	2021	[70]
	Nrf2	Inhibition of Nrf2 overcame OXA-resistance	OXA-resistant LS174T and SW480 cells	2018	[31]
		Nrf2 inhibition increased sensitivity to OXA by promoting ferroptosis and pyroptosis	HCT-116, LOVO cells and nude mouse xenograft model injected with HCT-116 cells	2023	[72]
		Inhibition of Nrf2 transcription under Dihydromyricetin treatment involved in prevention and reversion of OXA resistance	OXA-resistant HCT116 cells and nude mouse xenograft model	2021	[89]
	TCF4	F. nucleatum promoted the binding of transcription factor TCF4 on *GPX4* promoter and induced GPX4 upregulation.	Human specimens, HCT-116, HT29 cells and nude mouse xenograft model	2024	[42]
HCC	Nrf2, GPX4	Inhibition of LINC01134 promoted Nrf2-mediated GPX4 transcription, enhancing the OXA sensitivity via upregulation of ferroptosis	HepG2 cells with OXA resistance	2022	[94]
	DHODH	LOXL3-S704 phosphorylation prevented the ubiquitination of DHODH-K344, promoting the stability of DHODH and causing OXA-resistance via ferroptosis inhibition	Human specimens, PDX transplantation mice, *Loxl3-S704D* mutant mouse	2023	[98]
GC	SIRT1, GPX4, SLC7A11	Downregulation of DACT3-AS1 in CAFs-derived exosomes enhanced OXA-resistance via miR-181a-5p/SIRT1 signaling pathway	Human specimens; AGS, MKN7, MKN45, HGC-27 cells; nude mouse xenograft model(HGC-27 cells)	2023	[101]
	SCD1	AKAP8L promoted SCD1 expression, thus inhibiting ferroptosis and facilitating OXA-resistance	Human specimens; OXA resistant BGC-823 and MKN-45 cells, and nude mouse xenograft model	2022	[59]

OXA: Oxaliplatin; MTTP: Microsomal triglyceride transfer protein; PRAP1: proline-rich acidic protein 1; SLC7A11: solute carrier family 7 member 11; GSH: glutathione; GPX4: glutathione peroxidase 4; Nrf2: Nuclear factor erythroid2-related factor 2; F. nucleatum: Fusobacterium nucleatum; DHODH: dihydroorotate dehydrogenase; LOXL3: lysyl oxidase-like 3; DACT3-AS1: disheveled binding antagonist of beta catenin3 antisense1; AKAP8L: PRKA kinase anchor protein 8L; SCD1: Stearoyl coenzyme A desaturase-1; SIRT1: sirtuin 1; CRC: colorectal cancer; HCC: hepatocellular carcinoma; GC: gastric cancer.

present therapies based on ferroptosis to overcome OXA resistance.

2. Mechanism of ferroptosis

2.1. GPX4 defending system

In different diseases, multiple antioxidant systems including solute carrier family 7 member 11 (SLC7A11)-GSH (glutathione)-glutathione peroxidase 4 (GPX4), dihydroorotate dehydrogenase (DHODH)- dihydroubiquinone (CoQH2), ferroptosis inhibitory protein 1 (FSP1)-CoQH2, and GTP cyclohydrolase-1 (GCH1)- tetrahydrobiopterin (BH4) axes have been identified to play against ferroptosis [11,17,26–29]. However, SLC7A11-GSH-GPX4 axe distinguished itself as the most critical one in OXA resistance of cancer cells, as mounting reports illucidate the role of GPX4 and its upstream regulators in OXA resistance of cancer cells.

The SLC7A11-GSH-GPX4 defending system, one of the cellular antioxidant systems that neutralizes lipid peroxides directly, is closely related to metabolism of amino acids and forms the major cellular system against ferroptosis [16,45,46]. SLC7A11, also known as xCT, is the core component of system Xc^-, and controls the transport of extracellular cystine and intracellular glutamate, with cysteine acting as a rate-limiting precursor for the biosynthetic activity of GSH [47]. It was found that the inhibiting SLC7A11 would lead to the occurrence of ferroptosis in many cancers [37–39,48]. On the other hand, GPX4, the key inhibitor of ferroptosis, is responsible for the oxidation of two GSH to oxidized glutathione (GSSG) [16]. Downregulation of this key molecule also triggers ferroptosis. Interestingly, GPX4 is indicated to be regulated by complex mechanisms including epigenetic, transcriptional, and post-translational modifications [49].

2.2. Iron metabolism pathway

Compared to non-cancer cells, cancer cells have a strengthened demand on iron consumption, which entails them higher sensitivity to iron-dependent cell death, ferroptosis [50]. Iron exists in cancer cells as ferrous iron (Fe^{3+}) or ferric iron(Fe^{2+}), which is mediated by the cellular labile iron pool (LIP) constituted by multiple iron-containing compounds [51,52]. During ferroptosis, “free” irons directly catalysed the formation of toxic hydroxyl radical via Fenton reaction and accelerated cell death of cancer cells [53]. Therefore, the

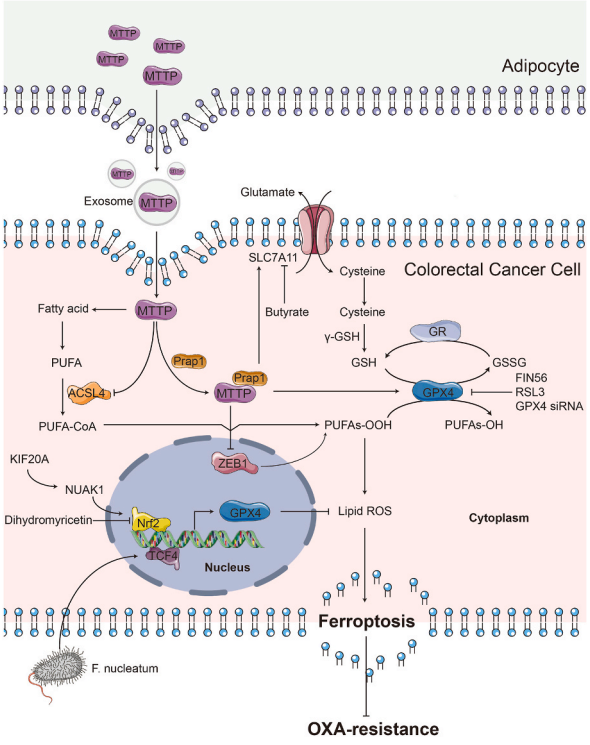

Fig. 1. The molecular mechanisms of ferroptosis in OXA-resistance of colorectal cancer. MTTP derived from adipocyte, transmits to CRC cells through exosomes. In CRC cells, increased MTTP acts with Prap1 to inhibit ZEB1 function. Both increased MTTP and inhibited ZEB1 promotes the production of PUFAs-OOH, thus inhibiting ferroptosis and enhancing OXA-resistance. On the other hand, inhibition of Nrf2 via NUAK1 silence, Dihydromyricetin or Nrf2 agonist, suppresses the transcription of GPX4. Besides, GPX4 inhibition via FIN56 or GPX4 siRNA, and downregulation of SLC7A11 by butyrate could also suppress the antioxidant functions. Under F. nucleatum, more TCF4 binds on *GPX4* promoter and induces GPX4 upregulation. These biological processes contribute to the occurrence of ferroptosis and thus inhibiting OXA-resistance of CRC.

cellular uptake and storage of iron in cancer cells might be critical in the OXA resistance process, and therapies targetting LIP levels may be promising in alleviating OXA resistance of cancer cells.

2.3. Lipid metabolism pathway

Similar to higher demands on irons, cancer cells also require stronger lipid metabolism to promote the prolifiation of cancer cells, which make cancer cells more suspectable to ferroptosis [54]. Since the introduction of ferroptosis [12], mounting evidence have indicated the interaction between lipid metabolism and ferroptosis [55–57]. Produced by oxidation of PUFA-containing phospholipids (PUFA-PLs), iron-dependent lipid peroxides (LPO) is fundamental for ferroptosis and determines the response of cancer cells to OXA. Among the regualtors that mediate lipid metabolism of ferroptosis, acyl-CoA synthetase long-chain family member 4 (ACSL4) and steroyl CoA desaturase 1(SCD1) have been suggested to mediate the sentitivity of cancer cells to OXA [58,59]. However, compared to GPX4 defending system or regulators of iron metabolism, the research focusing on the specific role of lipid metabolism pathway in OXA resistance of cancer cells seem to be less to our knowledge.

3. Colorectal cancer

Colorectal cancer, for which OXA was firstly approved for clinical treatment, was the third most deadly cancer globally with an estimated 1.97 million new cases in 2020 [60,61]. In the past decade, OXA resistance has become an urgent problem in the treatment of CRC patients [62], and multiple lines of evidence suggest that ferroptosis is largely involved in this biological process [32,63]. More specifically, the SLC7A11-GSH-GPX4 axis, one of the main cellular defense systems against ferroptosis, was identified to be widely participated in OXA resistance of CRC (Fig. 1).

3.1. GPX4-dependent regulatory network in OXA resistance of CRC

GPX4 is a glutathione peroxidase that converts lipid hydroperoxides into lipid alcohols, thereby suppressing lipid peroxidation and inhibiting ferroptosis [64–67]. Upregulation of intracellular GPX4 may suppress the therapeutic effect of cisplatin drugs via triggering cell resistance to ferroptosis and finally leading to tumor resistance to chemotherapeutic agents [68]. Increased GPX4 expression has been found in CRC cells and inhibition of GPX4 shows promising effects in reversing OXA resistance [63,69,70]. Additionally, in tumor tissues of advanced CRC patients, higher GPX4 levels were also identified compared to the paracarcinoma tissues [71]. In 2023, Huang et al. found that OXA reduced the expression of GPX4 in CRC cells [72]. The above results suggest a potential correlation between GPX4 and OXA resistance.

FIN56 and RSL3 are two ferroptosis inducers whose function is to promote the degradation of GPX4 [73] or inhibit the activity of GPX4 [74]. Interestingly, inhibition of GPX4 by FIN56 or GPX4 siRNA led to the occurrence of ferroptosis in OXA-resistant cell lines (Ht-29 and Caco-2) with accumulated lipid ROS levels [63]. Similarly, application of RSL3 increased the intracellular level of LIP, induced ROS accumulation, and finally increased the sensitivity of CRC resistance cell lines to OXA. Furthermore, the above-mentioned effects could be reserved by two ferroptosis inhibitors, liproxstatin-1 and deferoxamine [69]. In addition, upregulation of kinesin-like family member 20A (KIF20A), a microtubule-associated motor protein [75], has been reported to increase the intracellular GPX4 level to keep the redox balance via the KIF20A/NUAK1/Nrf2/GPX4 axis, and inhibit the ferroptosis process, eventually leading to cell resistance to OXA [70]. As GPX4 serves as an central factor in defending ferroptosis during OXA resistance, studies focusing on the upstream regulation mechanism of GPX4 or drugs targeting GPX4 have become the hot-spot in the field.

3.1.1. SLC7A11 inhibiton alleviates OXA resistance

SLC7A11 is a 12-pass transmembrane protein, and lower SLC7A11 expression was identified in the clinical tumor tissues from OXA responders compared to OXA non-responders, suggesting that suppression of SLC7A11 expression could enhance the effects of OXA treatment [76]. In CRC, SLC7A11 was found to be upregulated by the Microsomal triglyceride transfer protein (MTTP)/proline-rich acidic protein 1 (PRAP1) complex, thereby reducing ferroptosis susceptibility and promoting chemoresistance to OXA [58]. Increased MTTP expression was found in the adipose-derived exosomes from CRC patients who had a high body fat ratio. Via suppressing zinc finger E-box binding homeobox 1 (ZEB1) expression and increasing GPX4 and SLC7A11levels, MTTP/PRAP1 complex led to a reduced PUFA ratio and lipid reactive oxygen species (ROS) levels. In addition, MTTP also inhibited the expression of ACSL4, thus decreasing PUFA-CoA levels. To sum, MTTP served as an inhibitor for ferroptosis and reduced the sensitivity of CRC to OXA treatment [58].

In 2024, Di et al. introduced a previously unrecognized role of p53-SLC7A11 regulaetd ferroptosis in overcoming OXA resistance [44]. *TP53* gene has been widely studied in multiple cancers, and p53 protein has been identified as a transcription factor which inhibits SLC7A11 expression and thus regulating ferroptposis [77]. Radical fringe (RFNG) is one of the three fringes who are glycosyltransferases and play important roles in the Notch signaling pathway [78–80]. RFNG promotes OXA resistance of HCT116 and LS174T cells, and deleption of RFNG effectively improved the sensitivity of CRC cells to OXA. Furthermore, phosphorylated RFNG S255 (pS255) binds to nuclear importin proteins, enhance their tranlocation to the nucleus and eventually suppresses the phosphorylation of p53, thus upregulating SLC7A11 expression [44]. As p53 is an essential regulator in the cell cycle arrest of cancer cells and participates in the apoptosis process of cancer cell [81]. Here, Di et al. also found that apoptosis also accompanies with the ferroptosis process of CRC cells in response to OXA [44], which hints that ferroptosis only serves as one of the many reasons for OXA resistance and the crosstalk between ferroptosis and other biological process including apoptosis may be meaningful.

HCT116 cell is a well-known cell model for studying OXA resistance. Produced by microbial fermentation of dietary fibers, butyrate

is a four-carbon short-chain fatty acid [82]. Co-administration of OXA and butyrate, significantly inhibited the growth of tumor and promoted the lipid peroxidation in HCT116 tumor-bearing mice compared to OXA monotherapy alone [76]. Notably, butyrate also induced lower levels of SLC7A11 in OXA-treated mice and promoted the pro-ferroptotic function of OXA. This finding is consistent with previous reports that SLC7A11 dysregulation may contribute to platinum resistance in cancer patients [83,84]. In conclusion, inhibition of SLC7A11 may potentially alleviate OXA resistance and other chemoresistances including platinum resistance.

3.1.2. Nrf2-mediated GPX4 in OXA resistance of CRC

Nuclear factor erythroid2-related factor 2 (Nrf2) is a transcription factor of the cap'n'collar (CNC) family and/or the CNC-bZIP proteins [40,41,85]. Nuclear accumulated Nrf2 promotes the transcription of GPX4 and other antioxidant factors [86]. Due to the crosstalk of ROS and Nrf2 signaling pathways in carcinogenesis, Nrf2 modulation has been recognized as an important event in the ferroptosis process and related cancer therapies including overcoming OXA resistance [31,72,87–89].

Previously, it was suggested that OXA inhibits the viability of CRC cells through the Nrf2 regulating pathway [88]. In CRC patients with HER2 overexpression, Nrf2 inhibition has been confirmed as an important strategy to overcome OXA resistance [31]. In 2023, Huang et al. found that Nrf2 deleption enhanced the inhibition effect of OXA on the growth of HCT116 xenograft tumor in vivo [72], suggesting that inhibition of Nrf2 improved the sensitivity of CRC cells to OXA by promoting ferroptosis and offering a novel target for alleviating chemoresistance in CRC. In addition, it's notable that the silence of NUAK1 inhibited the nuclear transport of Nrf2 and the expression of GPX4, enhancing ferroptosis and blocking OXA resistance [69,70]. Dihydromyricetin (DMY) is a flavonoid compound from the Chinese medicinal herb Vitis heyneana. Recently, transcription of Nrf2 was also reported to be effectively inhibited by DMY, which showed potential in the prevention and reversion of OXA resistance in CRC [89].

In summary, Nrf2 is a ubiquitously expressed transcription factor whose downregulation would inhibit the expression of GPX4 and therefore overcome the OXA resistance of CRC. Increased Nrf2 levels may contribute to OXA resistance by enhancing the transcription of antioxidant factors in tumor tissues. In addition, nuclear translocation of Nrf2 is also associated with decrease LIP levels to prevent the additional production of ROS, which inhibits the occurrence of ferroptosis and promotes OXA-resistance [36]. The specific mechanism of this process underlying OXA resistance of CRC remains to be explored.

3.1.3. Gut microbiome links TCF4-GPX4 axis with OXA resistance

Gut microbiome dysbiosis is one potential cause for OXA-resistance [90]. In 2024, Li et al. nominated that Fusobacterium (F.) nucleatum, a tumor-pro bacterium, promotes OXA resistance through inhibiting ferroptosis of CRC cells, which build connection between ferroptosis mediated OXA resistance and gut microbiome [42]. In CRC patients who carry more abundance of F. nucleatum, CRC is tend to relapse and develop OXA-resistance. Mechanistically, F. nucleatum induces GPX4 upregulation via contributing to binding of transcription factor TCF4 on *GPX4* promoter, which was in line with Lv's report of TCF4-GPX4 axis mediating ferroptosis in CRC [91]. Althrough TCF4 has been reported to involve in the immunotherapy resistance of melanoma [92] and participate in the ferroptosis process of multiple cancers including gastric cancer and breast cancer [6,7], the connection between gut F. nucleatum and TCF4, the transcription factor of GPX4, provides unique perspectives for ferroptosis-mediated OXA resistance of CRC.

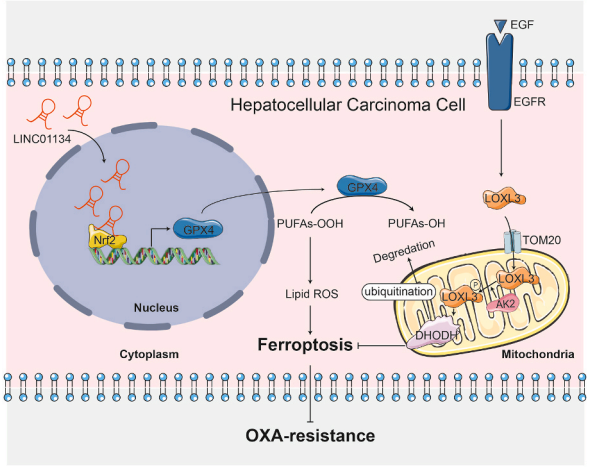

Fig. 2. The molecular mechanisms of ferroptosis in OXA-resistance of Hepatocellular Carcinoma. In HCC cells, increased LINC01134 promotes the recruitment of Nrf2 to the promoter of GPX4 and enhances the transcription of GPX4, inhibiting ferroptosis. Under EGF–EGFR signaling, TOM20 interacts with LOXL3 and promots its translocation into mitochondria, in which, AK2 mediates the phosphorylation of LOXL3. Later, phosphorylated LOXL3 prevents the ubiquitination of DHODH, promoting the stability of DHODH to resist ferroptosis. The above biological processes confer the OXA-resistance of HCC.

4. Hepatocellular carcinoma

Hepatocellular carcinoma (HCC) was the most common form of liver cancer, with which over 900,000 people were diagnosed worldwide [93]. As the first chemotherapy drug for advanced HCC worldwide, OXA is one of the most commonly used chemotherapy drugs for HCC patients [94]. However, OXA resistance has become the leading cause for treatment failure. In recent years, emerging evidence indicated that ferroptosis was the key mechanism in regulating the process (Fig. 2).

4.1. LINC01134/Nrf2/GPX4 regulating OXA resistance in HCC

Nrf2 is a key regulator in the antioxidant response of ferroptosis [72] and therefore may participate in the ferroptosis-related OXA resistance of HCC. Early in 2015, Sun et al. reported that Nrf2 was essential in protecting HCC cells from ferroptosis. Genetic deletion or pharmacological inhibition of Nrf2 promoted the anticancer activity of erastin and sorafenib against HCC both in vivo and in vitro [95]. The above findings suggest the possible involvement of Nrf2-regulated ferroptosis in the regulation of OXA resistance of HCC.

LncRNA involves in multiple biological processes of cancers, including chemoresistance and ferroptosis [96]. In 2022, a novel lncRNA, LINC01134, which is positively associated with poor prognosis of HCC patients, was found to promote the recruitment of Nrf2 to the promoter of GPX4 and thus exert the transcriptional regulation of GPX4, and inhibition of LINC01134 could significantly promote the accumulation of lipid ROS and malondialdehyde, and reduce the GSH/GSSG ratio, eventually enhancing the OXA sensitivity of HCC via upregulation of ferroptosis [94]. In summary, the LINC01134/Nrf2/GPX4/axis can regulate the OXA resistance of HCC. Therefore, therapies targeting LINC01134, inhibitors of Nrf2 or GPX4 could be practical treatment strategies for HCC patients with OXA resistance.

4.2. LOXL3 restrains mitochondrial ferroptosis to promote OXA resistance of liver cancer

The lysyl-oxidase family plays a major role in the reconstruction of the extracellular matrix (ECM) and participates in the cross-linking of collagen and elastic fibers [97]. In this family, LOXL3 was recently identified to contribute to the chemoresistance of liver cancer through ferroptosis [98]. Regulated by EGF–EGFR signaling, TOM20 interacted with LOXL3 and promoted its translocation to mitochondria, leading to mitochondrial LOXL3-S704 phosphorylation via adenylate kinase 2. In mitochondria, LOXL3

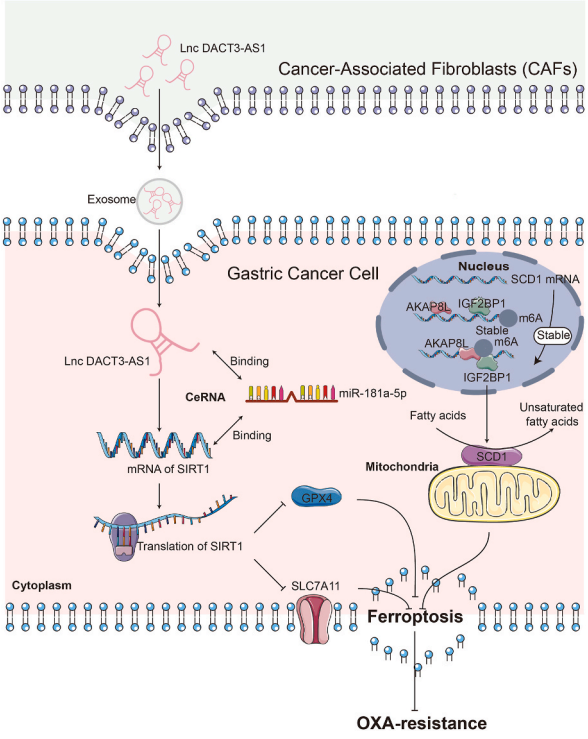

Fig. 3. The molecular mechanisms of ferroptosis in OXA-resistance of gastric cancer. LncRNA DACT3-AS1 derived from cancer-associated fibroblasts (CAFs), transmits to GC cells through exosomes. In GC cells, increased lnc DACT3-AS1 directly targets MiR-181a-5p, which serves as the sponge of SIRT1 mRNA, promoting the translation of SIRT1. SIRT1 upregulation inhibits the expression of GPX4 and SLC7A11, therefore suppressing ferroptosis. AKAP8L interacts with the mRNA of SCD1 and enhances its stability via IGF2BP1-dependent manner, thus increasing the expression of SCD1, which transfers fatty acids into unsaturated fatty acids and inhibits the occurrence of ferroptosis. The above biological processes confer the OXA-resistance of GC.

contributed to resisting lipid peroxidation and ferroptosis caused by OXA. More importantly, LOXL3 deficiency sensitives liver cancer cells to low-dose OXA, which increases the tumor-killing efficacy. Mechanistically, LOXL3-S704 phosphorylation prevents the ubiquitination of DHODH-K344, which in turn promotes the stability of DHODH to resist ferroptosis by reducing CoQ to CoQH2 in the mitochondria. Eventually, the above process promoted cell survival under OXA treatment, resulting in increased chemoresistance [98].

Based on the above findings, DHODH inhibition has been proposed to overcome the OXA resistance of liver cancer [98], which also enhances the interaction between ferroptosis and OXA resistance. As expected, the combination of LOXL3-S704D mutation and DHODH inhibitor Leflunomide [99] significantly inhibited tumor growth in mouse liver, while LOXL3-S704D mutant mice were still potentially resistant to OXA [98].

5. Gastric cancer

5.1. DACT3-AS1 sensitized gastric cancer to OXA through miR-181a-5p/SIRT1 mediated ferroptosis

Gastric cancer (GC) was the most common malignancies in the world and the third leading cause of cancer-related deaths [100]. In 2023, Qu et al. reported a novel lncRNA named disheveled binding antagonist of beta catenin3 antisense1 (DACT3-AS1), which was derived from cancer-associated fibroblasts (CAFs) [101]. DACT3-AS1was mainly transferred to GC cells *via* exosomes, and eventually conferred ferroptosis-mediated OXA sensitivity to GC cells both *in vivo* and *in vitro* (Fig. 3) [101]. The expression of DACT3-AS1 was downregulated in the tumor tissues of GC patients, and predicted the poor prognosis of GC patients. Furthermore, decrease of DACT3-AS1 was shown to promote the malignant behaviors of GC cells in vivo and in vitro [101]. After being transmitted to GC cells via exosomes, DACT3-AS1 directly targeted MiR-181a-5p, which served as a SIRT1 sponge.

In the past decade, SIRT1 has been suggested to be involved in the ferroptosis of various diseases [102–105]. In OXA-resistant tumors, DACT3-AS1 was downregulated, and miR-181a-5p was increased, which eventually inhibited the translation of SIRT1 via a competitive endogenous RNA mechanism. However, overexpression of SIRT1 elevated the proportion of lipid ROS, induced ferroptosis and inhibited cell viability in OXA-treated cells, with downregulated GPX4 and SLC7A11 as well as reduced GSH levels, while Fer-1, one ferroptosis inhibitor, corrected the inhibition effect of DACT3-AS1, confirming that DACT3-AS1 functioned as a potential regulator of ferroptosis [101]. Importantly, the miR-181a-5p mimic suppressed the ferroptosis biological process induced by DACT3-AS1. Eventually, downregulation of DACT3-AS1 in CAFs-derived exosomes enhanced the OXA resistance of GC. The above results demonstrated that exosomal DACT3-AS1 entails sensitivity of GC cells to OXA treatment via miR-181a-5p/SIRT1 regulated ferroptosis.

Table 2
Summary of drugs targeting ferroptosis in regulating OXA-resistance.

Drug	Production process	Mechanism	Target of ferroptosis regulator	Cancer type	Publication Year	Reference
DFMC	Ultrasmall Fe_3O_4 nanoparticles, Mn^{2+} ions, and CB-839 are integrated into dendritic mesoporous silica nano-particles	Catalyzing the decomposition of hydrogen peroxide into hydroxyl radical, and promoting lipid peroxides formation; Depleting existing GSH, and contributing to ROS-mediated tumor catalytic therapy; Introducing of CB-839 (glutaminase inhibitor) to promote the performance of GSH depletion;	GSH formation	Colorectal cancer	2022	[115]
PCN-Oxpt/PEG	Modifying OXA prodrug and PEG on Fe (III)-porphyrin metal-organic frameworks	GSH was dramatically consumed during the generation process of OXA from the prodrug; Internalized OXA promoted the production of H_2O_2 and Fenton reaction; OXA caused the ICD, enhanced IFN-γ production and influenced GPX4 activity	Consumption of GSH; H_2O_2 production and Fenton reaction; GPX4 activity	Breast cancer	2022	[17]
siProminin2@PSN-FeNP	Biocompatible hybrid nanoparticles containing iron oxide nanoparticles, siProminin2 and OXA	Inhibiting exosomal iron efflux to enhance ferroptosis; Induction of oxaliplatin-induced ICD;	Iron	Breast cancer	2022	[114]

DFMC: DMSN/Fe3O4−Mn@CB-839 nanomedicine; PCN-Oxpt/PEG: oxaliplatin prodrug and PEG co-loaded Fe(III)-porphyrins MOFs nanoplatform; siProminin2@PSN-FeNP: biocompatible hybrid nanoparticles composed of the iron oxide nanoparticles, polymers with oxali-platin attached, and siProminin2; ICD: immunogenic cell death.

5.2. Potential role of SCD1 in OXA resistance via ferroptosis

SCD1 is the fatty enzyme converting saturated fatty acids into monounsaturated fatty acids, which serves as a critical player of the fatty acid metabolic pathway and has been indicated to regulate the ferroptosis of multiple cancer cells including CRC, GC, pancreatic cancer, ovarian cancer and lung cancer [106–111]. Elevated SCD1 levels protect cancer cells from ferroptosis [112]. Recently, SCD1 was reported to facilitate OXA resistance of GC both in vivo and in vitro via PRKA kinase anchor protein 8L (AKAP8L) [59]. The above findings suggest the potential role of SCD1-regulated ferroptosis in reversing OXA resistance in GC (Fig. 3). By comparison of gene expression between chemoresistant and chemosensitive GC specimens collected from GC patients, AKAP8L was found to play an essential role in the stemness and chemoresistance of GC. Moreover, AKAP8L interacts with the mRNA of SCD1 and modulates SCD1 mRNA stability in an IGF2BP1-dependent manner, which provided evidence of SCD1 as a potential therapeutic target in the treatment of GC patients who were OXA chemoresistant [59]. Previously, SCD1 was shown to facilitate the anti-ferroptosis of GC cells [111]. Although no research has elucidated the specific relationship between SCD1, OXA resistance, and ferroptosis in GC yet, their crosstalk seems to be addressed in the near future. It's notable that SCD1 has been demonstrated to be essential in the ferroptosis of ovarian cancer, pancreatic cancer, lung cancer and CRC, which might provide suggestions for the study in GC concerning this topic [106,109,110,113].

6. Ferroptosis based therapies for reversing OXA resistance

Given the essential involvement of ferroptosis in OXA resistance of multiple cancers, emerging novel therapies targeting ferroptosis have been proposed and developed [17,114,115] (Table 2). In this section, we mainly introduced available methods to overcome OXA resistance by regulating ferroptosis.

6.1. GSH depletion therapies

The formation of GSH and lipid peroxides is a key event in ferroptosis and has been shown to contribute to OXA resistance in various tumor types. Therefore, therapies targeting the production of GSH or lipid peroxides may represent effective methods for reversing OXA resistance [116]. In 2022, Wu et al. developed a peroxidase-like active nanomedicine with dual GSH depletion property, which triggered the occurrence of ferroptosis in CRC cells and xenograft mouse model, thus reversing OXA resistance [115]. Using dendritic mesoporous silica nano-particles (DMSNs) as nanocarriers, ultrasmall Fe_3O_4 nanoparticles, Mn^{2+} ions, and Telaglenastat (CB-839), a glutaminase inhibitor [117], are integrated to form DMSN/Fe3O4−Mn@CB-839 nanomedicine with the name DFMC [115].

Under acidic conditions, DFMC also exhibits peroxidase-like activities, catalyzing the decomposition of hydrogen peroxide into hydroxyl radicals, and promoting lipid peroxide formation, which is necessary for ferroptosis. In addition, this nanomedicine also reduces the existing GSH and contributes to ROS-mediated tumor catalytic therapy. Meanwhile, the endogenous synthesis of GSH is blocked by the introduced glutaminase inhibitor CB-839, which further promotes the performance of GSH depletion. The biological process described above ultimately reduces OXA excretion from tumor cells and overcomes OXA resistance. Overall, the introduction of DFMC by Wu et al. provided insights for antitumor therapies to reverse OXA resistance via ferroptosis-related mechanisms, which are expected to provide ideas for the development of nanomedicine in the future.

6.2. Combination of OXA and ferroptosis enhancers

The combination of chemotherapy, ferroptosis, and immunomodulation shows a synergistic effect in inhibiting cancer progression, providing new ideas for overcoming drug resistance in traditional chemotherapy. In 2023, Hu et al. presented a nano platform constructed by modifying OXA prodrug and PEG on Fe (III)-porphyrin metal-organic frameworks (PCN(Fe) MOFs) [17]. Via the iron ions released from the MOFs, intracellular H_2O_2 in the tumor was converted into hydroxyl radicals, which triggered the occurrence of ferroptosis of cancer cells. The nano platform not only triggered ferroptosis but also increased its lethal effects. During the generation process of OXA from the prodrug, GSH was dramatically consumed. Meanwhile, internalized OXA promoted the production of H_2O_2 and the Fenton reaction, one of the key processes in ferroptosis [17,118]. In addition, OXA-induced immunogenic cell death (ICD) also increased the production of IFN-γ and inhibited the activity of GPX4, one of the essential anti-ferroptosis systems [17,94]. In summary, the combination of triple-enhanced ferroptosis, OXA-mediated chemotherapy, and ICD offers great prospects for overcoming the shortcomings of traditional therapies, including chemoresistance.

6.3. Anti-exosomal iron efflux therapy

Exosomes derived from tumor cells have been reported to influence the proliferation and metastasis of multiple cancers [119–121]. Interestingly, exosomes have been reported to export iron under a high intracellular iron concentration, leading to ferroptosis resistance [114]. Therefore, inhibition of iron container exosomes may be effective in inducing ferroptosis, suppressing tumor progression, and overcoming OXA resistance. Previously, it was suggested that the pentaspan membrane glycoprotein (Prominin2) could regulate intracellular iron efflux via exosomes [122]. Recently, biocompatible hybrid nanoparticles containing iron oxide nanoparticles, siProminin2, and OXA were constructed. Under the triple therapy strategy, siProminin2 successfully inhibited the secretion of tumor cell-derived exosomes and maintained intracellular iron levels, thereby enhancing ferroptosis [114]. With immunotherapy of OXA and

iron oxide nanoparticles, the hybrid nanoparticles combine ferroptosis and OXA-mediated immunotherapy, opening new opportunities to improve traditional chemotherapy and overcome chemoresistance.

7. Conclusions

In the present review, we mainly summarize current knowledge of ferroptosis in participating OXA resistance in multiple cancers including CRC, HCC, and GC. Key mechanisms of ferroptosis including GPX4 pathways and their upstream regulators, SLC7A11, Nrf2, and TCF4, deeply involved in the biological process of OXA resistance of multiple cancers. It is notable that these molecules also participate in the chemoresistance of other antitumor drugs including platinum and cisplatin. In addition, changes of LIP caused by Nrf2-GPX4 activity also contribute to OXA resistance. Currently, emerging studies focus on the upstream regulators of GPX4 and elucidate the potential crosstalks between them and OXA resistance. Comared to the GPX4-related studies, reports on other antioxidant systems against ferroptosis seems limited, and we look forward to seeing future studies concerning the topic.

The specific role of p53 in ferroptosis-mediated OXA-resistance should be emphasized. As a transcription factor, p53 has been widely studied in multiple mechanisms of caner cells. It is notable that p53 transcriptionally inhibited SLC7A11 expression and thus regulating ferroptosis and eventually OXA resistance of cancer cells. As p53 also plays other many roles in the biological process of cancer cells, the ferroptosis role of p53 in OXA resistance might be ignored or be covered by other mechanisms.

The function of lncRNA in OXA resistance is also emphasized in the present review, which is another spotlight of our study. In particular, LINC01134 promotes the recruitment of Nrf2 to the promoter of GPX4 and thus exerting transcriptional regulation of GPX4, which eventually enhanced the OXA sensitivity of HCC via upregulation of ferroptosis. On the other hand, a novel lncRNA named disheveled binding antagonist of beta catenin3 antisense1 (DACT3-AS1) sensitizes gastric cancer (GC) cells to OXA through miR-181a-5p/SIRT1 mediated ferroptosis.

LOX3 is a newly identified OXA-resistance contributor of liver cancer. Via S704 phosphorylation, LOX3 prevents the ubiquitination of DHODH-K344, promoting the stability of DHODH to resist ferroptosis by reducing CoQ to CoQH2 in the mitochondria, which eventually caused the increased chemoresistance. Importantly, this work enriches the mechanism between DHODH-CoQH2, another essential cellular antioxidant systems against ferroptosis, and OXA-resistance. In addition, it is also notable that SCD1 whose connections with OXA resistance and ferroptosis have been built. Although the critical demonstration of SCD1 regulated OXA resistance via ferroptosis has not been reported yet. We are looking forward to seeing the concerning reports.

Therapies targeting ferroptosis to reverse OXA resistance are also discussed in detail. Importantly, novel therapies based on ferroptosis have gained promising effects in overcoming OXA resistance, which might be the focus in the cancer field in the near future. Currently, nanomedicine with multiple functions covering ferroptosis enhancer and OXA induced chemotherapy are the mainstream, which displays promising effects in overcoming OXA resistance, as these nanomedicines offer synthetic effects rather than simple one-plus-one. Herein, we also suggest therapies targeting the above molecules, combination between ferroptosis inhibitor/promoter and traditional anti-cancer drugs like OXA, bringing positive impact for cancer patients, however, which was not fully studied to our knowledge.

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CRediT authorship contribution statement

Sijia Zhong: Conceptualization, Investigation, Visualization, Writing – original draft, Writing – review & editing. **Zihan Wang:** Conceptualization, Writing – original draft, Writing – review & editing. **Jiaxi Yang:** Writing – original draft, Writing – review & editing. **Di Jiang:** Writing – original draft, Writing – review & editing. **Kewei Wang:** Supervision, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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